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U. S. ARMY MEDICAL RESEARCH & NUTRITION LABORATORY

FUNDAMENTAL PARAMETERS INFLUENCING THE ACCUMULATION AND ELIMINATION OF CARBON MONOXIDE BY ADULT HUMAN BEINGS

UNITED STATES ARMY
MEDICAL RESEARCH AND DEVELOPMENT COMMAND

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Task No. [illegible] Physiological Studies of Carbon Monoxide

FUNDAMENTAL PARAMETERS INFLUENCING THE ACCUMULATION AND ELIMINATION OF CARBON MONOXIDE BY ADULT HUMAN BEINGS

OBJECT:

To devise the basis of a mathematical system for accumulation: elimination of carbon monoxide by human beings.

SUMMARY:

During the past two decades various types of experiments have been published by different schools of investigators dealing especially with the accumulation of carbon monoxide and its combination with hemoglobin in adult human beings. The various parameters which influence carbon monoxide accumulation, as well as its elimination, have not been completely understood or adequately described. This may perhaps have occurred because of particular interest in one, or at the most two, out of several parameters. When, however, a fairly complete set of parameters are derived, it becomes possible to develop a mathematical system of accumulation:elimination which can be tested with data published by several laboratories. The system can be solved by a person acquainted with algebraic methods, and one is able to predict the level of carboxyhemoglobin as a function of time from the initial level of carboxyhemoglobin, the concentration of inspired carbon monoxide and oxygen, expiratory flow rate, total body hemoglobin, and total pressure of gas breathed. These findings suggest that future physiological investigations, using carbon monoxide as a tracer, should include the measurement of further parameters than often included to date. Examples are given of the method of calculation, and this is used to illustrate the importance of each parameter. Although scarcely any data are available on elimination of carbon monoxide, it is further shown how the system may predict the rate of elimination, especially when using the newest method of treating carbon monoxide poisoning by means of artificial ventilation with pure oxygen at a total ambient pressure of two atmospheres.

RECOMMENDATIONS:

None.

APPROVED:

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INTRODUCTION

As the industrial revolution advances and spreads, more carbon monoxide than formerly becomes produced through the incomplete combustion of carbon compounds. Indeed, it would well be true that the chances of exposure to carbon monoxide poisoning have been increasing ever since the time of the first firemaker. With the advent of modern physiology it soon was pointed out by Claude Bernard that carbon monoxide has a greater affinity than oxygen for hemoglobin. Its consequent toxicity, being much like that of anemic anoxia, attracted the attention of physiologists interested in, among other things, the hazards of coal mining and other industrial and engineering operations (1). Automotive vehicles used in recent wars produce carbon monoxide, and in the absence of adequate ventilation this gas can accumulate in the vehicle. Many tests pertaining to military aspects of carbon monoxide were published in 1945 - 1946 (2). Just recently, about one-third of 186 victims of fatal crashes in the U. S. Air Force had tissue and blood saturation levels in excess of 30 per cent carboxyhemoglobin even in the absence of fire and more especially when flying at altitudes where a considerable proportion of cabin air would have been breathed (3). During 1954 - 1956 carbon monoxide poisoning accounted for 310 admissions for medical treatment in the U. S. Army. There were 97 deaths due to carbon monoxide. These figures are lower than actual because, if exposure had occurred in moving vehicles, the cases would have been reported as some type of motor vehicles accident (29). The indicated title of a Russian report can be cited as showing interest in carbon monoxide poisoning in outer space travel (30).

What levels of carboxyhemoglobin are dangerous? Even non smokers have traces of carboxyhemoglobin. In those who smoke much tobacco the carboxyhemoglobin often ranges from 5 to 8 per cent of their total hemoglobin, and this can rise to 12 per cent in persons who smoke heavily for two-thirds or more of a day. Brief breathing of air rich in carbon monoxide and then continuing for up to six hours on a more dilute mixture will maintain a level of 15 per cent carboxyhemoglobin in a recumbent subject at a simulated altitude of 15,000 feet (4). A heavy smoker (JL), who was a skillful observer, started this test with a level of 6.8 per cent carboxyhemoglobin which soon rose to 15 per cent. He reported no symptoms during the first hour, "but thereafter appeared headache which became progressively more severe, increasing and almost constant nausea, mental confusion, restlessness, pallor, cold extremities and a state of mild shock. These symptoms increased in severity as time passed". The carboxyhemoglobin level was always close to 15 per cent, and the combined oxyhemoglobin and carboxyhemoglobin level was 83 per cent, thus leaving 17 per cent as reduced hemoglobin on the systemic arterial side. Another subject (RR), while at 10,000 feet and at a level of 15 per cent carboxyhemoglobin suffered from "steadily increasing headache and recurrent nausea" during the final hours of exposure, even though in this case the combined arterial oxygen and carbon monoxide saturation was 97 per cent. At sea level with nearly complete arterial saturation with oxygen and carbon monoxide, J. S. Haldane considered that a brief exposure achieving 30 per cent carboxyhemoglobin was dangerous to himself, especially if engaged in exercise (1). Some valuable observations were reported by Smith and Sharp while using their improved method of treating carbon monoxide poisoning (5). Here, the carbon monoxide is removed with great rapidity

by causing the affected patient to breathe pure oxygen through a mask at a total ambient pressure of two atmospheres. On arrival, one of their patients, a 19 year old woman, "was breathing spontaneously and all reflexes were present, but she could be roused only with difficulty ... A man, aged 47, ... was in a deep coma, ashen-grey, with widely dilated pupils and spasticity of the upper limbs. Spontaneous respiration was absent and no pulse could be detected ... (He) would normally have been classified as moribund". The carboxyhemoglobin was 26 per cent in the woman and 50 per cent in the man soon after the time of arrival. In general it appears that carboxyhemoglobin levels of 15 per cent should be avoided, especially if maintained for a prolonged period of time during which complete mental alertness is required.

Advantage has been taken of the physiological properties of carbon monoxide. Tracer quantities were used in the first successful measurements of blood volume in living human beings, and with Sjöstrand's unique refinements this method continues to be used (6). The alveolar pressure of oxygen was estimated approximately from the distribution of carbon monoxide between inspired air and arterial blood (1). In recent years many physicians have become interested in gaseous diffusion between the lungs and the blood (7). From basic kinetic data, together with rates of accumulation, Roughton in 1945 deduced that at rest the duration of exposure of capillary blood to alveolar air was three-quarters of a second involving 60 ml of blood (8).

Although much information had been gathered during a century of study, the assumption was nearly always made that carbon monoxide was neither produced nor destroyed in the living body. In 1949, using the

long-lived $C^{14}O$, it was shown that mice could oxidise this to $C^{14}O_2$ (9). In the same year it was reported that the catabolism of hemoglobin produces carbon monoxide (10). Green plants, algae and even dry leaf powders, when wetted, make carbon monoxide in the presence of sunlight and oxygen (11). Such opposing reactions and their rates apparently have not been considered in so far as these can influence levels of blood carboxyhemoglobin. In what follows it is proposed to examine the chief events affecting a system which describes both the accumulation and elimination of carbon monoxide. Certain predictions can be made, and these can be checked with the results obtained in previous studies of adult human beings.

DERIVATIONS

<u>Steady State Equilibria of COHb = x_0.</u> Upon being exposed to air containing a fractional concentration of carbon monoxide ($F_{I,CO}$), the quantity of CO inspired per minute ($\dot{V}_I F_{I,CO}$) equals the total of that which is expired ($\dot{V}_E F_{E,CO}$), that which enters the body ($\dot{V}_{CO}$) and that which builds up at a certain rate to a definite concentration in the functional residual capacity of the lungs ($V_F \dot{F}_{A,CO}$).

$$\dot{V}_I F_{I,CO} = \dot{V}_E F_{E,CO} + \dot{V}_{CO} + V_F \dot{F}_{A,CO} \; . \; . \; . \; . \; . \left[\text{ml min}^{-1}\right].$$

This is also true for all other inspired gases including oxygen

$$\dot{V}_I F_{I,O_2} = \dot{V}_E F_{E,O_2} + \dot{V}_{O_2} + V_F \dot{F}_{A,O_2} \; . \; . \; . \; . \left[\text{ml min}^{-1}\right].$$

The last term in each expression should be of particular interest to those who make transient analyses of single breaths (7). It is entirely possible, especially with dilute CO, under steady state conditions, that the last term could be neglected so far as concerns the accumulation and elimination of CO. The last term in the oxygen expression is negligibly small in most cases. Consequently, these last terms will be dropped at this point, although further mention is made of them in the discussion. Next, consider

that $\dot{V}_E P_{E,CO}$ is distributed between the lungs' gas exchanging space ($\dot{V}_A P_{A,CO}$) and their dead space ($\dot{V}_D P_{I,CO}$)

$$\dot{V}_E P_{E,CO} = \dot{V}_A P_{A,CO} + \dot{V}_D P_{I,CO}.$$

This also holds true for oxygen, and when introduced into the short forms of the first two expressions, the gas rates entering the body become

$$\dot{V}_{CO} = (\dot{V}_I - \dot{V}_D) P_{I,CO} - \dot{V}_A P_{A,CO} \quad \ldots\ldots\ldots\ldots (1)$$

$$\dot{V}_{O_2} = (\dot{V}_I - \dot{V}_D) P_{I,O_2} - \dot{V}_A P_{A,O_2} \quad \ldots\ldots\ldots\ldots (2)$$

The rates of entry of CO and O_2 into the body can also be viewed according to the following general equations,

$$\dot{V}_{CO} = D_{CO}(P_{A,CO} - P_{B,CO}) \quad \ldots\ldots\ldots \ [\mathrm{ml\ min}^{-1}]$$

$$\dot{V}_{O_2} = D_{O_2}(P_{A,O_2} - P_{B,O_2}) \quad \ldots\ldots\ldots \ [\mathrm{ml\ min}^{-1}]$$

in which the flux, either positive or negative, is dependent on the pulmonary diffusing capacities (D_{CO} and D_{O_2}) and the difference in pressure of the gas in the alveoli ($P_{A,CO}$ and P_{A,O_2}) and of that in pulmonary capillary blood ($P_{B,CO}$ and P_{B,O_2}). J. S. Haldane wrote that the pressures of CO and O_2 are interrelated: $P_{B,CO} = (x/my)P_{BO_2}$ where x is the fractional saturation of hemoglobin in arterial blood due to CO, y is that due to O_2, and m is a partition coefficient here accepted to be constant and equal to 230 (12). The Haldane relationship and the two equations immediately above are solved together resulting in the expression

$$\dot{V}_{CO} = D_{CO} \left[P_{A,CO} - (x/my)\,(P_{AO_2} - \dot{V}_{O_2}/dD_{CO})\right] \quad \ldots\ldots\ldots (3)$$

where the constant, $d = D_{O_2}/D_{CO} = 1.23$, accounts for the difference in diffusibility of O_2 and CO on the basis of molecular size (7). The gas pressures are then written as the product of the total ambient pressure and the fractional concentration of the particular gas, and the

symbol $S = D_{CO} - d^{-1}$ is introduced. Upon equating equations 1 and 3, the value of carboxyhemoglobin (x) can be stated. However, several approximations are necessary in order for x to be stated in terms of parameters which henceforth will be considered as fundamental. The first assumption that $y = 1 - x$, which implies that systemic arterial blood is fully saturated with CO and O_2, results in the expression

$$x = \left[1 + \frac{SF_{A,O_2} - d^{-1}(\dot{V}_I - \dot{V}_D)F_{I,O_2} + d^{-1}\dot{V}_A F_{A,O_2}}{SmF_{A,CO} - m(\dot{V}_I - \dot{V}_D)F_{I,CO} + m\dot{V}_A F_{A,CO}} \right]^{-1}$$

provided $\dot{V}_{O_2}$ is expressed as in equation 2. Next observe, whereas $\dot{V}_A = \dot{V}_E - \dot{V}_D$, only slight error is introduced by writing $\dot{V}_A = \dot{V}_I - \dot{V}_D$, and during steady state equilibrium of the single CO flux system $\dot{V}_{CO} = 0$, implying that $F_{A,CO} = F_{I,CO}$, whence the above expression can be written

$$x_{e,1} = \left[1 + \frac{SF_{A,O_2} - d^{-1}\dot{V}_A(F_{I,O_2} - F_{A,O_2})}{SmF_{I,CO}} \right]^{-1}$$

Concerning equation 2, the data of others (13,14) when plotted as in Figure 1 shows that $a = \dot{V}_{O_2}/\dot{V}_A = 0.0498$ (highly correlated, $r = 0.962$), which implies that $\dot{V}_{O_2}$ is directly proportional to $\dot{V}_A$ at $\dot{V}_{O_2}$ rates of less than 2,500 ml min^{-1}. These results show that $F_{A,O_2} = F_{I,O_2} - a$, both while at rest and during exercise when $\dot{V}_{O_2}$ rates are less than 2,500 ml min^{-1}.

From the above, it now becomes possible to write

$$x_{e,1} = (1 + \beta/\alpha) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (4)$$

where $\alpha = SmF_{I,CO}$ and $\beta = S(F_{I,O_2} - a) - d^{-1}\, a\, \dot{V}_A$. Further, from data on the same adult men and women as shown in Figure 2, $\dot{V}_A = 0.835\ \dot{V}_E - 1{,}120$ (very highly correlated, $r = 0.996$).

The equation for $r_{s,?}$ implicitly requires that, of the CO which enters and leaves the body, practically all of it combines with hemoglobin and that none is oxidized, hydrated, or otherwise broken down, or even produced, or else that such opposing rates are equal. Early tests with radioactive tracers employed $C^{11}O$ prepared in a cyclotron from B_2O_3. Because of the 21 minute half life of this isotope, the tests lasted for only one hour, and less than one-tenth per cent of the $C^{11}O$ which disappeared from the blood was expired as $C^{11}O_2$ (15). A contrary conclusion was later arrived at (9) by exposing mice in controlled tests in a 12.5 liter chamber initially containing close to 10 ml of CO gas together with traces of the long-lived $C^{14}O$. Depending on the number of mice, from one-half to two-thirds of the CO disappeared in the course of four days. The rate of conversion of $C^{14}O$ to $C^{14}O_2$ was reported to be 0.29 (10^{-3}) ml hr^{-1} g^{-1} of body weight. In tests of recovery of total CO following three hours of equilibration of fresh whole blood of rats, dogs and human beings (12), the rate of disappearance was 1.8 (10^{-3}) ml min^{-1} g^{-1} of total COHb. If in the mice tests the total hemoglobin was 0.01 of the body weight and this was one-third saturated with CO, the rate of conversion of $C^{14}O$ to $C^{14}O_2$ would have been 1.6 (10^{-3}) ml min^{-1} g^{-1} of total COHb.

Sjöstrand measured the small quantity of CO which was expired by adult human beings who breathed CO free air (10). He concluded, as Lemberg indicated on biochemical grounds, that the daily breakdown of hemoglobin produces CO. At a mol ratio of 4:1 with 1/120 of the total (ΣHb) hemoglobin producing CO daily, this could furnish 0.007? (10^{-3}) ml min^{-1} g^{-1} of hemoglobin. This rate, just recently verified (27), slightly opposes the oxidation rate discussed above. Thus, $\dot{V}_{CO,CO_2} - \dot{V}_{Hb,CO}$

becomes

$$\dot{V}_{Hb,CO,CO_2} = (rx - c)\sum Hb \; . \; . \; . \; . \; . \; . \; . \; . \; . \; [ml\ min^{-1}\ g^{-1}]$$

where x = the proportion of COHb, $r \cong 1.8\ (10^{-3})$, and $c \cong (0.0073)\ 10^{-3}$. At equilibrium under steady state conditions of the postulated triple flux system, $F_{A,CO} = F_{I,CO} - \dot{V}_{Hb,CO,CO_2}\ \dot{V}_A^{-1}$. Consequently, the equilibrium statement for the triple flux begins as

$$x_{e,3} = \left[1 + \frac{\beta}{\alpha - \gamma(rx_{e,3} - c)}\right]^{-1}$$

which takes the form of a quadratic equation

$$x_{e,3} = \frac{\alpha + \beta + \gamma(c + r)}{2\gamma r} - \left[\left(\frac{\alpha + \beta + \gamma(c + r)}{2\gamma r}\right)^2 - \frac{\alpha + \gamma c}{\gamma r}\right]^{1/2}$$

where α and β are defined under equation 4 and $\gamma = m(1 + s\dot{V}_A^{-1})\sum Hb$.

A definition of D_{CO} is required in order to complete both the single flux, $x_{e,1}$, and the triple flux, $x_{e,3}$, equations. It would be desirable to write this according to parameters already employed, such as rate of alveolar gas flow and total hemoglobin. Figure 3a shows a plot of average values of D_{CO} and $\dot{V}_A$ at rest and at exercise for individual men and women studied by other investigators (14, 17). In all cases, D_{CO} increases with $\dot{V}_A$. On the average, D_{CO} increases by 0.915 ml min^{-1} mm^{-1} of Hg when $\dot{V}_A$ increases by 1,000 ml min^{-1}. From this value of the slope, the mean intercept on the ordinate can be found for each person, thus indicating the value of D_{CO} when $\dot{V}_A = 0$. The values of the intercepts are high for large men, low for small men, and even lower for women of larger body surface area than some of the small men. Sjöstrand found for each square meter of surface area that men had 425 g of total hemoglobin whereas women had only 321 g of total hemoglobin (6). Figure 3b shows that, on the average, the intercepts on the

ordinate of Figure 3a increase in proportion with the quantity of $\sum$Hb as predicted from body surface area of men and women. This suggests on empirical grounds that in adult human beings

$$D_{CO} \cong 0.243 \sum Hb - 11.5 + 0.915 (10^{-3}) \dot{V}_A.$$

On theoretical grounds, Roughton and Forster (18) wrote that $D_{CO}^{-1} = D_M^{-1} + (\theta V_C)^{-1}$ from which of necessity it follows that $D_M > D_{CO}$ and that $V_C = \theta^{-1}(1 - r)^{-1} D_{CO}$ where $r = D_M D_{CO}^{-1}$. The mean value of θ^{-1} for six men breathing room air can be computed from their data to be close to 1.41. On the average, $r \cong 0.45$. When our prediction of D_{CO} is introduced, $V_C \cong 0.110 \sum Hb + 0.00234 \dot{V}_A - 29.4$. Because $\sum$Hb was not measured or reported by them, $V_C \cong 46.7\, A + 0.00234\, \dot{V}_A - 29.4$ where A is male body surface area in square meters. From this, if $\dot{V}_A \cong 5{,}000$, for their six subjects $\bar{V}_C = 69$ ml as compared with 59 ml by a steady state method in which they actually determined D_{CO} and θ. Of further interest, our prediction of D_{CO} allows V_C to increase with the types of exercise which cause $\dot{V}_A$ to increase (8). An idea of the precision is shown in Figure 4 which compares predicted values with those reported from three laboratories (18, 19, 20) in addition to the two laboratories (14, 17) from whose data the prediction equation was built. Here, the standard deviation of the difference is $\sigma_d = 5.0$. If that of actual measurements is $\sigma_m \cong 3.0$, it follows that for prediction the $\sigma_p \cong \sqrt{25 + 9} = 5.8$ which, though less precise than an actual measurement, is suitable for the present purposes. Among the parameters which influence D_{CO}, at least two of these of considerable importance are total body hemoglobin as well as rate of ventilation of the lungs during the change from rest to exercise.

To ascertain the validity of $x_{e,1}$ or $x_{e,3}$ recall that the 1946 Pensacola studies of the U. S. Navy (4) were performed by first breathing 0.7 to 2.0 per cent CO in air for about three minutes, until it was guessed that COHb levels were such as to be similar to those which eventually would have been achieved while breathing a more dilute mixture of CO in air. Once having thus reached a particular level of COHb, this was steadily maintained by breathing the dilute CO for periods of four to seven hours, during which arterial and venous levels of COHb were equal, fairly steadily maintained, and thus can be termed x_e, "measured". Table 1 lists basic data and the computed values of α, β, and γ for each of the total six tests on the three men. The filled circles in Figure 5 compare the $x_{e,1}$ values predicted from α and β with the x_e, "measured" values. The crosses in Figure 5 do the same for $x_{e,3}$ values from which it becomes obvious, if the triple flux system operates in human beings, that the opposing rates have similar values, i.e. $rx_{e,3} \approx c$ such that $\alpha \gg \gamma(rx_{e,3} - c)$. In support of this, Kruhøffer's experiments (16), that portion dealing with rate and the oxidation of $C^{14}O$, can be cited as showing that $r \approx 0.3\ (10^{-3})$ instead of $1.8\ (10^{-3})$. At this stage, $x_{e,1}$ seems perfectly satisfactory for the prediction of equilibrium levels of COHb under steady state conditions. Although granting the possibility that CO is produced and also destroyed by the living body, it becomes unnecessarily complicated when the influence of such processes are considered, as was done in the derivation of the equation for $x_{e,3}$.

Accumulation of carbon monoxide, i.e. $x(t)$ = COHb as a function of time. In the early 1940's suitable methods were devised for measuring low levels of COHb (19). These were employed in tests performed on adult human males, who mostly were physically qualified for military service. Because of the dangers involved, x was never allowed to rise

much beyond a level of one-third of the total available hemoglobin. In some laboratories only a single blood sample was withdrawn, usually from a vein, and this was done at a definite time from 3 to 300 minutes after starting to breathe a known dilution of CO in either air or "pure" O_2. Realizing that smokers began with a moderately high level of COHb, one laboratory withdrew two blood samples, one at the start and the other at the end of the test (21). Usually, the pressure was that at sea level. A few tests were made at the low pressures obtaining in chambers for the simulation of altitude. The subjects were seated, recumbent, and sometimes engaged in the exertion of "hard work". They wore a mask, tightly covering the nose and mouth, into which was delivered the desired gas mixture at a rate stated as expiratory flow. One laboratory reported the measured blood volume of each subject (19). Another guessed at the blood volume on the basis of an older method of prediction based on body surface area (21). The hematocrit was never reported, and only in one set of tests were the O_2 and CO capacity of a milliliter of blood actually measured and reported (4).

In other words, none of the tests obtained and reported measurements of all of the necessary parameters. Probably, those which in all cases were reliably reported are as follows: $F_{I,CO}$, F_{I,O_2}, $\dot{V}_E$, P, and x. In one case x_o was reliable (21); for the other case (19) we have guessed at x_o according to the memory of one of the subjects (FC) as to whether the others were smokers of tobacco. In one set of tests (19) the reported blood volume was perfectly suited for finding ΣHb except that the CO capacity was not listed, so we have assumed that each subject had a capacity of 0.2 ml of CO per ml of blood. For the other set of tests (21) we have used Sjöstrand's value of 425 g. of hemoglobin for

each square meter of male body surface (6). Further, certain parameters were never measured, and we have had to apply the interrelation of $\dot{V}_A$ and $\dot{V}_{O_2}$ with $\dot{V}_E$; very recently, similar interrelationships were published dealing with the control of respiration and circulation (22). However, the reader should realise that this may apply in rest and exercise but certainly not during hyperpnea. In the latter case the present study of a system is deficient for the accumulation and elimination of CO. The sole remaining parameter is D_{CO} which we derived above in order to complete expressions for $x_{e,1}$ and $x_{e,3}$. As a consequence of the way in which D_{CO} was correlated with $\dot{V}_A$ and ΣHb, it follows that the prediction of D_{CO}, though suitable for adult human beings, certainly should not be applied to infants, small children, and experimental animals which have ΣHb of 200 g. or less together with low values of $\dot{V}_E$. In order to write a more thorough prediction, there is need for further experiments on the actual values of D_{CO}, ΣHb, and $\dot{V}_A$.

It is easy to make the above critical remarks after having perused the findings of competent investigators who, while exploring the accumulation of CO, naturally placed more emphasis on some parameters and excluded others of less current interest. In recognition of this, in the tabulation of the results of 51 tests from the literature, we have indicated, where necessary, the assigned values (Tables 2 and 3). The reader who follows these tabulated values can compute or predict x and see this compared with the measured value (Figure 6).

The basis on which $x(t)$ can be predicted rests upon the approach of the accumulation reaction to a steady state equilibrium, $x_{e,1}$. Certainly this can not be ascertained from only one or two determinations

of x at a given time such that the maximum observed values of $x < 0.33$ $x_{e,1}$. Although there is little information for judging which order of a reaction pertains to accumulation, elimination of CO is claimed to be a first order reaction. From this it may be inferred that accumulation is also a reaction of the first order. Repeated statements have been published concerning the order of elimination (e.g. 2, 15). An especially clear presentation of data is that for a single subject (WWW), who undoubtedly eliminated CO in the order so claimed (23). The subject was certainly an interested person of experience who probably was able to keep $\dot{V}_B$ at a steady rate throughout the period of the one hour test during which x was measured at intervals by two experts (WSR and PJWR). These indications, together with the derived value of x_e, and the apparent linear relationship of x with time for the early stage of the process (2), dictated an attempt to write an exponential equation which describes x(t). The mathematical treatment begins with the general first order equation $x = A + Be^{-kt}$. The initial and equilibrium conditions determine the constants A and B, i.e. when $t = o$, $x = x_o$ and when $t = \infty$, $x = x_e$, resulting in the expression

$$x = x_e - (x_e - x_o)e^{-kt} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (5).$$

It is now necessary to define k, which determines the rate of the process, in terms of parameters that have been previously designated as fundamental. This begins with a linear approximation for $\dot{V}_{CO}$ during the first part of the accumulation. Various workers (19, 21) have noticed the resulting linear relationship, $x - x_o = \beta t$, and have substantiated it with their data.

A digression will clarify this linear relationship which ultimately will be solved simultaneously with equation 5 for $x - x_e = 1/3(x_e - x_o)$,

the one-third point being chosen because equation 5 is nearly linear for the first one-third of its range. $(x - x_o)$ indicates an increase of CO in the blood equal to $(x - x_o)s\Sigma Hb$ which, in turn, is equal to the quantity of CO inspired minus the quantity expired $(\int \dot{V}_I F_{ICO}\,dt - \int \dot{V}_E F_{ECO}\,dt)$, provided the buildup of CO in the lungs' functional residual capacity is neglected. If the linear approximation $\dot{V}_{CO}t = V_{CO}$ is employed, the integration of equation 1 gives

$$\dot{V}_{CO}t = (x - x_o)s\ \Sigma Hb$$

which implies that $\phi = \dot{V}_{CO}/s\Sigma Hb$. Next, a factor is inserted which will allow the pressure to be other than atmospheric at sea level, resulting in the expression

$$\phi = \frac{\dot{V}_{CO}\ f_p}{s\Sigma Hb}\ ,\ \text{where}\ f_p = \left[\frac{P - 47}{713}\right]$$

Using equations 1 and 2 and accepting $\dot{V}_I \cong \dot{V}_E$ and definitions of α, β, and Υ, $\dot{V}_{CO}$ can be rewritten thus:

$$\dot{V}_{CO} = (\alpha - \frac{x}{y}\ \beta)\Upsilon^{-1}\ \Sigma Hb.$$

Noting that $\dot{V}_{CO}$ is a function of x, ϕ is solved for a point when the process has completed one-third of its full range, i.e. when

$$x - x_o = 1/3\ (x_e - x_o)$$

At the one-third point

$$\phi_{1/3} = \frac{\alpha - b\beta}{\Upsilon s f_p^{-1}}\ ,\ \text{where}\ b = \left[\frac{3}{x_e + 2x_o} - 1\right]^{-1}$$

Returning to the first order equation 5, k can now be found by solving this equation and the established linear relationship for the above stated one-third point as indicated below.

$$t_{1/3} = (1/3)(x_e - x_o)(\phi_{1/3})^{-1}$$

$$(1/3)(x_e - x_o) + x_o = x_e - (x_e - x_o)\ e^{-k(t_{1/3})}$$

$$\therefore -k = \frac{\phi_{1/3}}{x_e - x_o} 3\ln 2/3$$

Having found an expression for k, it is inserted into equation 5, $\phi_{1/3}$ being replaced by its equivalent, and the constant term $\frac{3\ln 2/3}{s}$ being symbolized by h:

$$x = x_e - (x_e - x_o)e^{\frac{(\alpha - b\beta)f_p h}{(x_e - x_o)} t} \quad \ldots\ldots\ldots\ldots (6)$$

where, in review,

$a = \dot{V}_{O_2}\dot{V}_A^{-1} = 0.0498$

$m = 230$, partition coefficient

$s = 1.34$ ml of CO to saturate one gram of hemoglobin

$h = s^{-1}\ 3\ln 0.667 = -0.909$

$d = D_{O_2}D_{CO}^{-1} = 1.23$

$f_p = (P-47)\ 713^{-1}$, assuming dry gas is breathed at a pressure of P mm of Hg.

$b = \left(\frac{3}{x_e + 2x_o} - 1\right)^{1}$

$x_e = x_{e,1} = [1 + \beta/\alpha]^{-1}$

$\alpha = Sm\ F_{I,CO}$

$\beta = S(F_{I,O_2} - a) - d^{-1}a\ \dot{V}_A$

$\gamma = m(1 + S\dot{V}_A^{-1})\Sigma Hb$

$S = D_{CO}(P-47)$

$D_{CO} = 0.043\Sigma Hb - 11.5 + 0.915(10^{-3})\dot{V}_A$

$\dot{V}_A = 0.835\ \dot{V}_E - 1{,}120$

Predictions, according to equation 6, of the proportion of the total hemoglobin which would occur as carboxyhemoglobin are compared in Figure 6 with actual determinations reported in 5· tests carried out in two laboratories (Tables 2 and 3). Thirty-six tests (filled circles) were done at a total pressure of approximately one atmosphere

while breathing a mixture of CO and air (19, 21). Five tests (circles) were done at one atmosphere while breathing CO in 98 per cent O_2. Ten tests were done at total pressures of less than one atmosphere: in two of these, the pressure was so low as one-fifth of an atmosphere, and CO in 98 per cent O_2 was breathed (triangles); in eight of these tests the pressure exceeded one-fifth of an atmosphere and CO in air was breathed (filled triangles). Tables 2 and 3 show that each subject started the test with different levels of COHb, x_0, and during the exposure the COHb rose to a higher level, x, which is shown by the abscissa in Figure 6. The standard deviation of the difference between predicted and reported values of x is $\sigma_d = 0.015$. This would represent the precision of prediction if there were no error in the method of measuring the reported values of COHb. Gasometric methods, such as those used in the two laboratories, are more precise at low than at high levels of COHb. If so, it follows from $\sigma_p^2 = \sigma_d^2 + \sigma_m^2$ that a low levels $\sigma_p \cong 0.015$, whereas at higher levels, of e.g. 0.3 COHb, $\sigma_p \cong 0.020$. The mean deviation, $\bar{d} = 0.021$, combined with $\pm 2\sigma_p$, was used to draw the two dashed lines in Figure 6. The intercept on the ordinate of the uppermost line indicates that the 2σ precision of prediction is approximately 0.05 at the various levels of COHb involved in the total 51 tests. Of more importance, however, the predictions appear to be valid at different total pressures and concentrations of inspired O_2.

INFLUENCE OF FUNDAMENTAL PARAMETERS

In order to illustrate the influence of the fundamental parameters included in equation 6, it is believed advisable to show, with an example, how to compute x. Then, by graphic means, it is proposed to show the relative importance of each parameter (Figs. 7 - 11).

The procedure for calculating both x_e and x, although algebraic, is somewhat lengthy. An example, using likely values for the variables, will illustrate the procedure.

Given: $P = 760$ mm of Hg.

$\dot{V}_E = 10{,}000$ ml per minute

$F_{I,CO} = 0.001$ ml per ml

$F_{I,O_2} = 0.21$ ml per ml

$\Sigma Hb = 800$ gram

$x_o = 0.050$ proportionate initial saturation with CO.

Using the definitions set forth immediately following equation 6, it is found, to within three significant digits, that:

$$\dot{V}_A = (0.835)(10{,}000) - 1{,}120 = 7{,}230$$

$$\therefore D_{CO} = (0.045)(800) - 11.5 + (0.915)(7.23) = 29.5$$

$$\therefore S = (29.5)(710) = 21{,}000$$

α, β, γ can be determined using S and the various other equations and constants specified under equation 6.

$$\alpha = (21{,}000)(230)(0.001) = 4{,}830$$

$$\beta = (21{,}000)(0.210 - 0.0498 - \frac{(0.0498)(7{,}230)}{1.23}) = 3{,}070$$

$$\gamma = (230)(1 + \frac{21{,}000}{7{,}230})(800) = 719{,}000$$

Now, the desired predictions can be made.

$$x_e = \frac{1}{1 + \frac{3{,}070}{4{,}830}} = 0.611$$

Since $x_o = 0.050$, a value near that of a person who smokes moderately, the exponent of eq. 6 may be determined by using the values computed above of α, β, γ, recognizing that $f_p = 1.0$. Whence,

$$b = \frac{1}{\frac{2}{0.611 + 2(0.050)} - 1} = 0.311$$

and the exponent of equation 6 is

$$\frac{(\alpha - M)f_p h}{\gamma(x_e - x_c)} t = \frac{[4,830 - (0.611)(3,070)](1)(-0.909)}{719,000\ (0.611 - 0.050)} t = 0.00875t$$

Then, the level of carboxyhemoglobin at any time becomes

$$x = 0.611 - (0.611 - 0.050)e^{-0.00875t}$$

If t = 20 minutes

$$x_{20} = 0.611 - 0.561e^{-0.175}$$

Since the "natural" antilogarithm of -0.175 = 0.839

$$x_{20} = 0.611 - (0.561)(0.839) = 0.140.$$

It is thus seen that a large man with a moderate ventilation rate, when breathing room air at atmospheric pressure diluted to a level of one-tenth per cent carbon monoxide, could have a carboxyhemoglobin level of approximately 14 per cent saturation after 20 minutes of exposure.

The above type of example can be expanded to illustrate the influence of the various parameters. Allen and Root (12) determined the partition coefficient m at 37°C. using aerotonometers containing fresh whole blood mixtures such that within three hours equilibrium was approached from either direction. Further, the plasma hydrogen ion activity was caused to vary with CO_2. When the plasma pH was 7.30 to 7.36, the m value was 230. At lower and higher pH, i.e. 7.15 and 7.40, m fell to a value of 170. Sendroy does not believe that m is affected by plasma pH (24) and accordingly would treat m as constant and equal to close to 230, as has been done thus far for the purpose of simplification. Table 4 was prepared to show that if m were to vary from 170 to 230, this would cause steady state equilibria levels of carboxyhemoglobin, $x_{e,1}$, to range from 0.54 to 0.61. However, for at least two hours during approach to such

equilibria, the absolute values of carboxyhemoglobin would rise similarly. Even if m were to vary through this range, it would have little influence on $x(t)$ values for at least two-thirds of the total accumulation. It therefore seems reasonable to accept m as a constant and presently to ignore the claimed influence of plasma hydrogen ion activity.

On the basis of equation 6, various aspects of accumulation of CO are shown in Figures 7 through 10 which cite assigned dimensions in the legends. From Figure 7 it is clear that air containing 100 parts of CO per million would lead to a steady state equilibrium of 15 per cent COHb. If air contained 1,000 p.p.m., the $x_{e,1}$ value would rise to 61 per cent COHb. In contrast, if 98 per cent O_2 contained 1,000 p.p.m., the level would be 20 per cent. The above (Fig. 7) would also have been anticipated approximately by Haldane (1). It is doubtful, however, if the following Figure 8 could have been predicted by him and his colleagues, since full use of the presently derived equation 6 is involved. To reach 30 per cent levels of COHb, when breathing air, would require only 5 minutes if the air contained so much as 1 per cent CO. Sixty-five minutes would be required to reach this level if the air contained 0.1 per cent CO. If the air contained 0.01 per cent CO, it would take 120 minutes for the percentage COHb level to rise only from 2 to 6. The above would occur if the expiratory flow were maintained at an ambient rate of 10 liters per minute. At rates greater and less than this, the curves in Figure 9 show that the approach to steady state equilibrium would occur far more rapidly if the ventilation of the lungs were to increase. Figure 10 shows that with lesser quantities o. total body hemoglobin the rate of approach to steady state equilibrium would

increase. In t[illegible] CO to combine with 600 grams of net [illegible] saturation of 42 per cent. During a similar [illegible] grams of hemoglobin could combine with a larger [illegible] of CO, [illegible] the saturation would be slightly less than above and equal to [illegible] per cent. From these illustrations it appears that the most important parameter is $F_{I,CO}$ followed in descending order by F_{I,O_2} then $\dot{V}_E$ and finally ΣHb.

Although accumulation of CO can be viewed as set forth above and dangerous situations or at le[illegible] some of the fundamental parameters in physiological tracer experiments can be anticipated, it is wise to emphasize the elimination of CO from the body. This especially should be of interest to physicians who will find the observations of Smith and Sharp (5) to be predictable when using equation 6. Let us consider that their moribund male patient could have had a 60 per cent COHb level, i.e. in this case x_c = 0.60, at the start of the treatment at two atmospheres of ambient pressure. Further, accept their finding with the reversion spectroscope that, after one hour of treatment, his COHb $\cong$ 0. Oxygen was breathed through a mask, and $F_{I,O_2} \cong 0.98$. Suppose $F_{I,CO} = 10^{-5}$ or 10 p.p.m. If the artificial ventilation rate was 10 liters min^{-1} and the total body hemoglobin was [illegible] grams, all the necessary parameters have been assigned. Then equation [illegible] predicts the rapidly descending curve, drawn with a dashed line in Figure [illegible], which after 60 minutes of treatment, anticipates there to be 3 per cent COHb instead of "none". The adjacent curve indicates, with all parameters the same except that the ambient pressure is one atmosphere, that the rate of elimination would be 2.5 times more slow. The third of the dashed curves is of interest to aviation medicine, showing at one-half of an atmosphere

that breathing of 98 per cent oxygen would eliminate CO at a rate of 2.9 times slower than at one atmosphere. Similar effects of ambient pressure on elimination of CO would occur when breathing air, except that at a given pressure, the rate of elimination of CO would be 6.5 times more slow than when breathing 98 per cent oxygen (three continuous curves in Fig. 11). This six-fold relative difference is precisely that cited by Lilienthal (2) for findings in two laboratories. However, there truly were absolute differences in elimination half-time between the two laboratories. It is believed that such could have occurred if the subjects of Roughton and Root (25) might have had a low ventilation rate of 5 liters min^{-1}, whereas those of Lilienthal and Pine (cited in 2) might have had either a ventilation rate exceeding 5 liters min^{-1} or else a total body hemoglobin lower than 800 grams. Although it would be desirable to refer to other studies of elimination, such as from dogs (26), the present authors have earlier indicated that for equation 6 the derivation of D_{CO} and the interrelationship of $\dot{V}_{O_2}$ with $\dot{V}_A$ and $\dot{V}_E$ contain knowledge that could presently apply only to men and women. It therefore seems that the same fundamental parameters affecting the accumulation will operate just as effectively upon the elimination of CO from adult human beings.

DISCUSSION

A critique of the means employed to obtain a prediction of blood carboxyhemoglobin chiefly concerns the fact that, whereas it was possible to state certain fundamental parameters, it was impossible to find these as having been actually measured and reported in their entirety in the various cited experiments performed with human beings. It is indeed gratifying that, in the tests of predictability, the results on accumulation

(Fig. 6) and elimination of CO (Fig. 11) agreed as well as they did. This suggests, should future needs arise, that instead of making estimates of various parameters, it will become desirable to measure these with independent methods capable of detecting all of the necessary factors involved in the computation of a given parameter. The presently appreciated parameters can be listed according to decreasing order of absolute precision of mensuration ranging from errors of ± 0.5 per cent to ± 5 per cent, or somewhat more, as follows: $P_{\Sigma} - P_{H_2O}$, x_o, $F_{I,CO}$, F_{I,O_2}, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, ΣHb, $\dot{V}_A$, and D_{CO}. These, in part, are associated with the constants d and m. Further, in the true statement $x + y + z = 1$, it was convenient to let $z = 0$, where z is the proportion of total functional arterial hemoglobin occurring as reduced hemoglobin. It was not only convenient but also necessary because of lack of full information to interrelate certain of the above basic parameters, thus sacrificing some precision.

The error involved in equating $\dot{V}_I$ and $\dot{V}_E$ is negligibly small. Within fairly wide limits $\dot{V}_{O_2} = 0.0498\ \dot{V}_A$; if $\dot{V}_{CO_2} \cong 0.83\ \dot{V}_{O_2}$, it can be shown that $\dot{V}_I = 1.009\ \dot{V}_E$, thus eliminating the necessity of collecting information on $\dot{V}_{CO_2}$. Further, from the interrelation of $\dot{V}_{O_2}$ and $\dot{V}_A$ (Fig. 1), it becomes possible to dismiss, though with certain misgivings (hyperpnea, O_2 debt, etc.), the necessity of reporting values of $\dot{V}_{O_2}$. Hence, three basic parameters can be expressed in terms of $\dot{V}_A$ which is very closely related to $\dot{V}_E$ (Fig. 2), a parameter easily measured and often reported. Although specialized investigators to date have not reported on the relationship of D_{CO} with ΣHb and $\dot{V}_A$, their data are highly suggestive of such, at least to within a presently suitable

degree of precision which could certainly be improved in future studies. Therefore, the nine presently appreciated parameters decrease to six in number and consist of the following: P, x_0, $F_{I,CO}$, F_{I,O_2}, $\dot{V}_E$, and ΣHb. These certainly should be accurately measured and reported in studies using CO as a tracer. Among these, the only one which is difficult to comprehend is ΣHb because this obviously includes non-circulating hemoglobin (or its equivalent). Several schools of investigators have indicated that the non-circulating hemoglobin is about 15 per cent of the circulating hemoglobin. A means of reporting ΣHb would be to measure the total circulating hemoglobin by one of various methods and then multiply this by a factor of 1.15 (26).

Concerning the CO build-up in the functional residual capacity of the lungs, it was stated early in the above derivations that $\dot{F}_{ACO}$ approaches zero as the exposure time increases. The quantity of gas $\left(\int_0^t V_F \dot{F}_{ACO}\, dt = \left[V_F F_{ACO} \right]_{t = t} - \left[V_F F_{ACO} \right]_{t = 0} \right)$ which builds up the CO concentration in the lungs may be appreciable, especially if the inspired CO concentration is high. This is apparent when it is noted that at equilibrium $F_{A,CO}$ approximately equals $F_{I,CO}$, and that this particular equilibrium is rapidly approached in the lungs. If the exposure is of long duration, the quantity does not have much effect since it is small compared to the total CO in the blood. For high inspired concentrations necessarily having short exposure times, the quantity becomes significant. In most of the data referred to by the authors, the exposure times were probably sufficiently long to permit disregard of this quantity. In the few cases where the exposure times were short, the

data were such that estimation of this quantity was impossible. Hence, it was neglected, although a thoroughly complete system should contain the term, $\dot{V}_F P_{A,CO}$.

It was stated prior to equation 4 that $x + y = 1$. This would be true if the O_2 and CO pressures were sufficiently high so that hemoglobin became fully saturated with O_2 and CO on its passage through the lung capillaries, and a shunt never existed which bypassed these capillaries. The relationship should correctly be stated as $x + y + s = 1$ where s perhaps could be defined as functions of P_{A,O_2} and $P_{A,CO}$ together with a shunt factor. Altogether this would slightly affect the computation of $x_{e,1}$. For subject JL in Table 1, since $s = 0.17$, $x_{e,1} = \left[0.83 + 1.519/0.2615\right]^{-1} =$ 0.151 instead of the value 0.147 which was computed on the assumption that $s = o$. This subject had an exceedingly large proportion of reduced hemoglobin in the systemic arterial blood, due to his being exposed for several hours to a simulated altitude of 15,000 feet, yet the calculation of x_e is scarcely affected in this instance.

There have now been mentioned many refinements to the present system which certainly seem important. It was intended to make the system as simple as possible, and many approximations were necessarily made to keep it so. The present lack of measured parameters certainly could lead to inadequate interpretations. For example, when two possible refinements (the production and oxidation of CO) were included, the resulting expression for $x_{e,3}$ was much more complicated and did not agree with reported values. It is believed, however, that if all factors were taken into account, and the parameters necessary for their calculation were adequately determined, the complete system could be

improved beyond its present capabilities. The design and execution of experiments which should enable investigation of these various ideas are being considered. Minute quantities of $C^{14}O$ could be safely used, and its accumulation and elimination from the human body could be detected continuously with a vibrating reed electrometer.

ACKNOWLEDGMENT

This survey of selected literature and the building of a prediction system started at the recent annual meetings of the Federated Societies of Experimental Biology when Mr. Allan Claghorn (Linde Company), who has long been interested in standards for breathing gases, asked in brief "Would 100 p.p.m. of CO be dangerous to SCUBA divers or should this never exceed 20 p.p.m. ?" At a total of three atmospheres with an ambient flow of 10 liters min^{-1} a fairly large man starting at 2 per cent carboxyhemoglobin could reach an equilibrium level of 12.9 per cent when breathing 100 p.p.m. of CO. After 100 minutes of exposure the level would be only 3.4 per cent. After 1,000 minutes this would rise to 10.2 per cent. Carboxyhemoglobin levels so low as these could elevate the threshold for vision in dim light (28), but it is doubtful if other physiological functions would be seriously affected during periods of time spent in such diving.

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TABLE 1. Prediction of steady state equilibria, $x_{e,1}$ and $x_{e,3}$, and comparison with "measured" value (based on data of Lilienthal, Riley, Proemmel, and Franke, 4).

Subject	JL_1	JL_2	RR_1	RR_2	CF_1	CF_2
P	401	598	523	523	523	523
* $\dot{V}_A \cdot 10^{-3}$	10	10	10	10	10	10
* [illegible]	800	[illegible]	800	800	800	800
$F_{I,CO}$	10^{-4}	$1.5(10^{-4})$	10^{-4}	$0.5(10^{-4})$	$0.5(10^{-4})$	$0.5(10^{-4})$
F_{I,O_2}	0.2193	0.2105	0.2048	0.2084	0.2065	0.2084
$S \cdot 10^{-3}$	11.35	17.7	15.3	15.3	15.3	15.3
a	0.0498	0.0498	0.0498	0.0498	0.0498	0.0498
$\alpha \cdot 10^{-3}$	0.2615	0.611	0.352	0.176	0.176	0.176
$\beta \cdot 10^{-3}$	1.519	2.439	1.967	2.022	1.993	2.022
$\gamma \cdot 10^{-6}$	0.393	0.510	0.466	0.466	0.466	0.466
$x_{e,3}$	0.110	0.161	0.116	0.060	0.061	0.060
$x_{e,1}$	0.147	0.200	0.152	0.080	0.081	0.080
meas. x_e	0.151	0.235	0.145	0.086	0.075	0.073
x_o	0.068	0.068	0.011	0.011	-	-
t	365	260	400	313	345	305
Symptoms	Yes	-	Yes	-	-	-

* Values assigned by present authors but not given by investigators.

TABLE 2. Prediction of COHb as a function of time, x, in nineteen brief tests performed on five men at three different pressures, with a ten-fold range in alveolar gas flow and when breathing either air or oxygen containing as much as 5,000 parts per million of CO (based on data of Forbes, Sargent, and Roughton, 19).

Subject	P mm Hg	$\dot{V}_A (10^{-3})$ ml min^{-1}	ΣHb g	F_{I,O_2} ml ml^{-1}	$F_{I,CO} (10^{-3})$ ul ml^{-1}	t min	$x_{e,t}$	x_o	pred. x	reported x
JB	760	5.73	762	0.21	3.41	6	0.841	0.05	0.143	0.120
FK	"	7.06	851	0.21	4.05	"	0.869	"	0.173	0.146
FK	"	7.06	911	0.21	4.05	"	0.863	0.01	0.126	0.117
WF	"	6.81	865	0.21	2.79	"	0.812	"	0.090	0.090
WF	"	3.77	"	0.206	3.00	10	0.822	"	0.099	0.111
WF	"	4.09	"	0.98	"	"	0.422	"	0.087	0.092
FC	"	3.79	1,017	0.206	"	"	0.821	"	0.090	0.099
FC	"	4.77	1,017	0.98	"	"	0.428	"	0.087	0.093
WF	"	23.9	866	0.208	1.10	16	0.661	"	0.199	0.228
WF	"	25.6	"	0.98	1.25	6	0.242	"	0.080	0.072
JB	"	36.5	762	0.208	1.27	4.5	0.709	0.05	0.152	0.134
JB	"	39.0	"	0.98	"	4.2	0.247	"	0.113	0.0[illegible]
FK	"	52.3	851	0.208	1.49	3	0.746	"	0.115	0.10[illegible]
FK	"	39.0	"	0.98	1.46	12	0.2[illegible]	"	0.207	0.182
FK	412	9.9	"	0.21	3.56	6	0.864	"	0.107	0.112
FK	"	10.8	911	"	"	"	0.862	0.01	0.073	0.067
JB		10.7	762	"	3.87	"	0.870	0.05	0.123	0.117
JB	140	8.4	"	0.98	4.94	"	0.583	"	0.058	0.077
WF	"	7.7	866	"	"	"	0.578	0.01	0.019	0.048

x_o not given by investigators; assigned by present authors on the basis of whether or not the subjects smoked tobacco.

Table 3. Prediction of COHb as a function of time, x, in tests lasting up to 300 minutes on thirty-two men at two different pressures when breathing air with so little as 90 parts per million of CO (based on data of Pace, W. V., Consolasio, White and Behnke, 21).

Subject	$\dot{V}_A(10^{-3})$ ml min^{-1}	ΣHb g	$P_{I,CO}(10^3)$ ml ml^{-1}	t min	$x_{e,1}$	x_o	pred. x	reported x
MAR	6.9	875	2.0	20	0.755	0.022	0.191	0.145
COV	4.4	796	"	"	0.753	0.016	0.142	0.112
KLI	4.0	817	"	"	0.752	0.000	0.114	0.107
HOL	3.7	706	"	"	0.753	0.040	0.157	0.130
BLA	13.8	761	"	"	0.770	0.004	0.302	0.346
KRU	16.8	854	"	"	0.771	0.013	0.326	0.346
TUB	19.1	862	"	"	0.773	0.033	0.365	0.323
MCB	17.9	883	"	"	0.771	0.029	0.355	0.349
SCB	14.8	777	"	"	0.771	0.036	0.337	0.337
BIT	24.0	1,002	1.5	24	0.719	0.017	0.331	0.349
SCA	18.5	777	"	20	0.722	0.037	0.302	0.358
DEN	13.6	740	1.0	30	0.627	0.069	0.289	0.289
DIB	14.7	777	"	"	0.628	0.024	0.241	0.270
BRI	13.2	731	"	"	0.627	0.050	0.290	0.26[illegible]
PIT	14.3	861	1.72	15	0.738	[illegible]	0.236	0.230
WED	17.5	830	1.87	"	0.760	0.072	0.308	0.265
WAG	14.5	749	2.18	"	0.787	0.042	0.304	0.338
SHA	19.7	905	1.42	20	0.707	0.064	0.301	0.261
CAT	13.8	805	1.41	"	0.702	0.054	0.255	0.261
JAM	16.5	747	1.29	"	0.690	0.008	0.229	0.248
UTS	13.5	713	0.90	30	0.604	0.0[illegible]	0.220	0.247
LEG	14.4	800	0.90	30	0.601	0.049	0.266	0.236

Table 3 (Cont'd)

Subject	$\dot{V}_A (10^{-3})$ ml min^{-1}	ΣHb g	$F_{I,CO} (10^3)$ ml ml^{-1}	t min	$x_{e,1}$	x_0	pred. x	reported x
KIN	14.0	7?8	0.94	30	0.612	0.089	0.278	0.295
SPE	11.9	714	0.55	45	0.478	0.036	0.183	0.193
WAR	13.4	683	0.56	"	0.488	0.030	0.196	0.254
RHI	15.8	795	0.57	39	0.491	0.018	0.179	0.200
WAT	6.7	752	0.92	30	0.592	0.018	0.139	0.121
SAN*	5.8	740	0.09	240	0.129	0.000	0.045	0.063
SCH*	5.2	795	"	180	0.126	0.033	0.055	0.078
FRC*	5.8	816	"	270	0.127	0.004	0.046	0.073
AUD*	5.7	786	0.18	300	0.226	0.058	0.130	0.165
HAY*	4.6	710	"	"	0.225	0.035	0.110	0.150

*P = 523 mm Hg = 10,000 ft. standard altitude with $\dot{V}_A$ shown as the flow at that altitude; all other subjects were at sea level; ΣHb was assigned to be 425 g $(m^2)^{-1}$.

Table 4. Variation in the partition coefficient, m, and its slight effect on anticipated levels of carboxyhemoglobin, x(t).

m	x_e	x_{10}	x_{40}	x_{120}
170	0.538	0.095	0.206	0.384
190	0.565	0.096	0.210	0.396
210	0.590	0.096	0.213	0.406
230	0.611	0.097	0.215	0.415

Given: F_{I,O_2} = 0.21, $F_{I,CO}$ = 0.001, P = 760 mm Hg, $\dot{V}_E$ = 10,000 ml min^{-1}, ΣHb = 800 grams, and x_0 = 0.050.

LEGENDS OF FIGURES

Fig. 1. Relationship between rates of oxygen utilization and of alveolar ventilation in men and women during rest and exercise (based on data of Filley *et al* 13 and Turino *et al* 14)

Fig. 2. Relationship between rates of alveolar and expiratory flow in men and women during rest and exercise (based on data of Filley *et al* 13 and Turino *et al* 14)

Fig. 3.a) Diffusing capacity of the lungs for carbon monoxide compared with alveolar flow rate (based on data of Turino *et al* 14 and Bates *et al* 17, taking mean values during rest and exercise of their men and women subjects).

b) Relationship between diffusing capacity and total hemoglobin (estimated according to Sjöstrand, 6) when alveolar flow approaches zero

Fig. 4. Comparing predicted diffusing capacities for carbon monoxide with those reported from three laboratories (Forster *et al.*, Tables 2 and 3, ref. 18; Forbes *et al.* Table 5, ref. 19; [illegible] *et al*, Table III, ref 20).

Fig. 5. Comparing the predictions of steady state equilibria achieved by a single flux of carbon monoxide, $x_{e(1)}$, and a triple flux ($x_{e(3)}$), with "measured" values of x_e (based on data of Lilienthal *et al*, 4)

Fig. 6. Prediction of blood carboxyhemoglobin as a proportion of total hemoglobin while breathing either air or oxygen mixtures containing traces of carbon monoxide both at sea level and at simulated altitudes (based on data of Forbes *et al* 19 and Pace *et al.*, 21)

Fig. 7. Steady state equilibrium levels of carboxyhemoglobin, $x_{e(1)}$, at various concentrations of inspired carbon monoxide in air and [illegible] per cent oxygen. Given: $\dot{V}_E$ = 10,000 ml min^{-1}, P = 760 mm Hg, ΣHb = 800 grams, and x_0 = 0.02

Fig. 8. Accumulation of carboxyhemoglobin as a function of time, x(t), when breathing various concentrations of carbon monoxide in air at $\dot{V}_E$ = 10 000 ml min^{-1}, P = 760 mm Hg, ΣHb = 800 grams, and x_0 = 0.02. Note that for purposes of visual comparison Figs 8 through 10 are drawn to the same scale

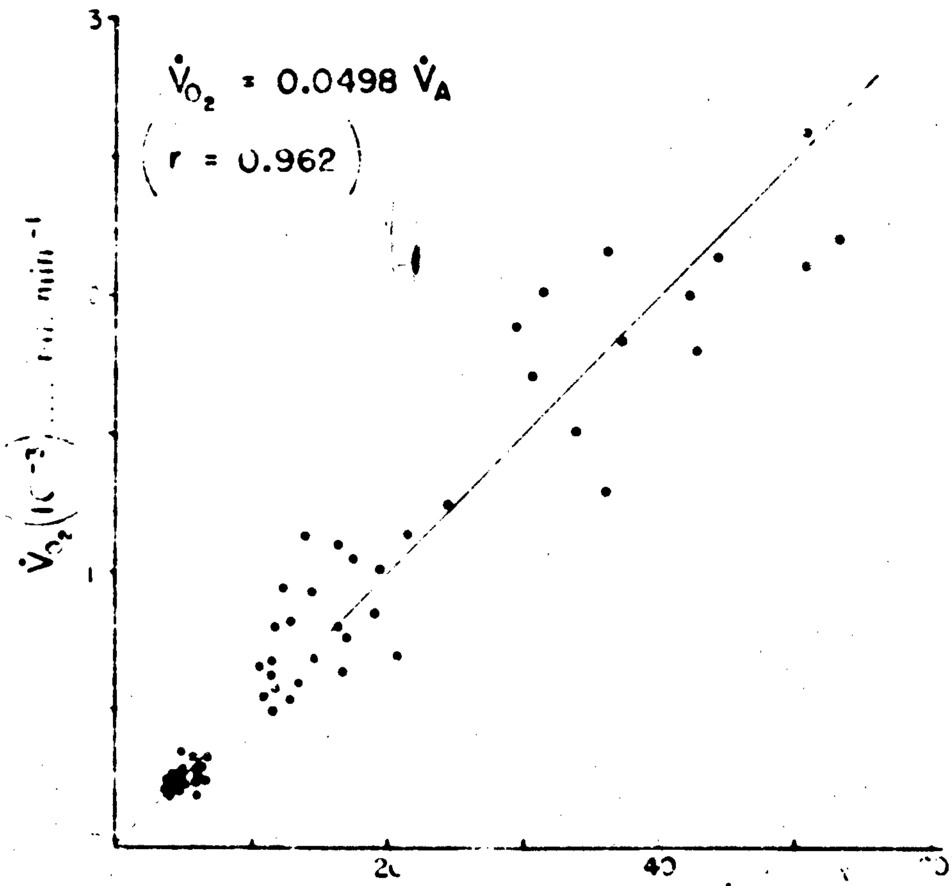
Fig. 9. Accumulation of carboxyhemoglobin as a function of time, x(t), when breathing at different flow rates. Given: $F_{I,CO} = 10^{-3}$, F_{I,O_2} = [illegible], P = 760 mm Hg, ΣHb = 800 grams, and x_0 = 0.02.

Fig. 10. Accumulation of carboxyhemoglobin as a function of time, $x(t)$, in accordance with different quantities of total body hemoglobin in grams. Given: $F_{I,CO} = 10^{-3}$, $F_{I,O_2} = 0.21$, $\dot{V}_g = 10{,}000$ ml min^{-1}, $P = 760$ mm Hg, and $x_o = 0.02$.

Fig. 11. Elimination of carboxyhemoglobin as a function of time, $x(t)$ when breathing air or 98 per cent oxygen at three different total ambient pressures. Given: $F_{I,CO} = 10^{-5}$, $F_{I,O_2} = 0.21$ or 0.98, $P = 0.5$, 1, or 2 atmospheres, $\dot{V}_g = 10{,}000$ ml min^{-1}, $\Sigma Hb = 800$ grams, and $x_o = 0.60$.

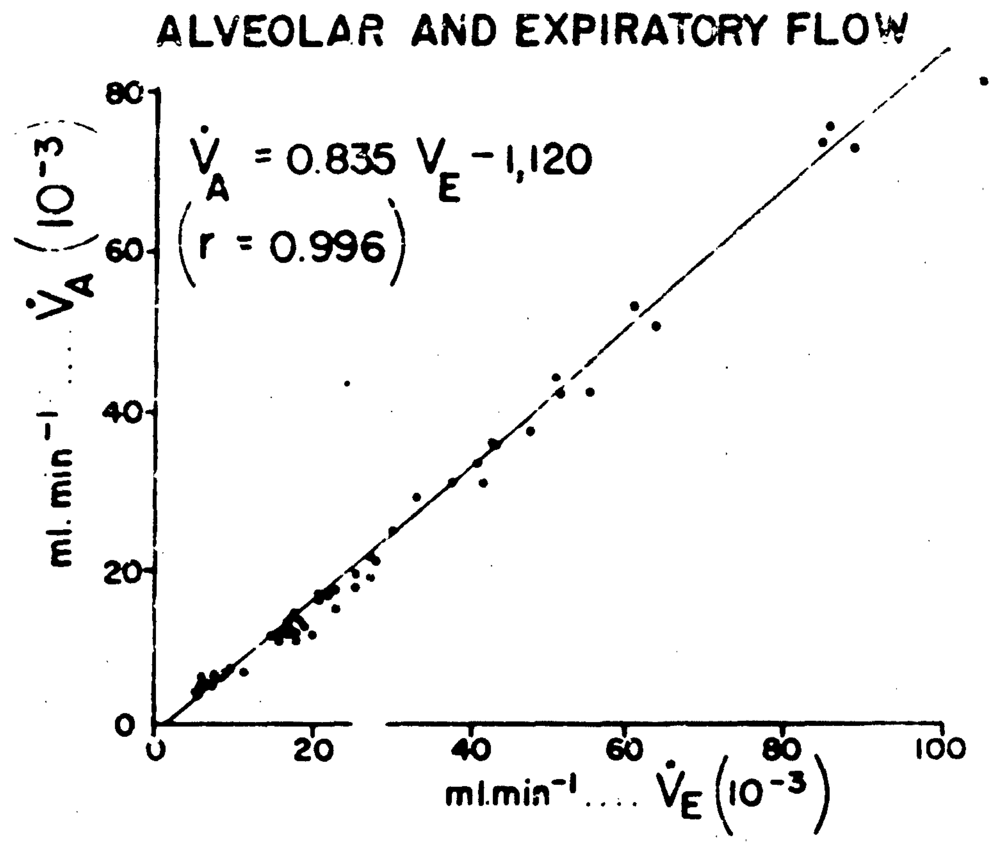
FIG. 1

OXYGEN UTILIZATION AND ALVEOLAR VENTILATION



DURING REST AND EXERCISE

FIG. 2



ALVEOLAR AND EXPIRATORY FLOW
$\dot{V}_A = 0.835\ V_E - 1{,}120$
$(r = 0.996)$
ml. min^{-1} .... $\dot{V}_A$ (10^{-3})
0
20
40
60
80
100
ml.min^{-1}.... $\dot{V}_E$ (10^{-3})

METHOD OF PREDICTION OF DIFFUSING CAPACITY

FIG. 3a

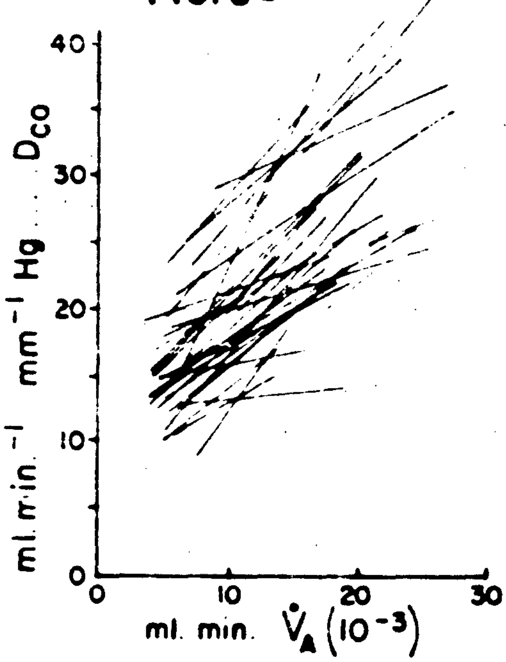


FIG 3b

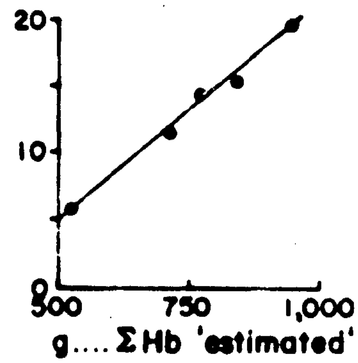


FIG. 4

PREDICTED AND REPORTED DIFFUSING CAPACITY

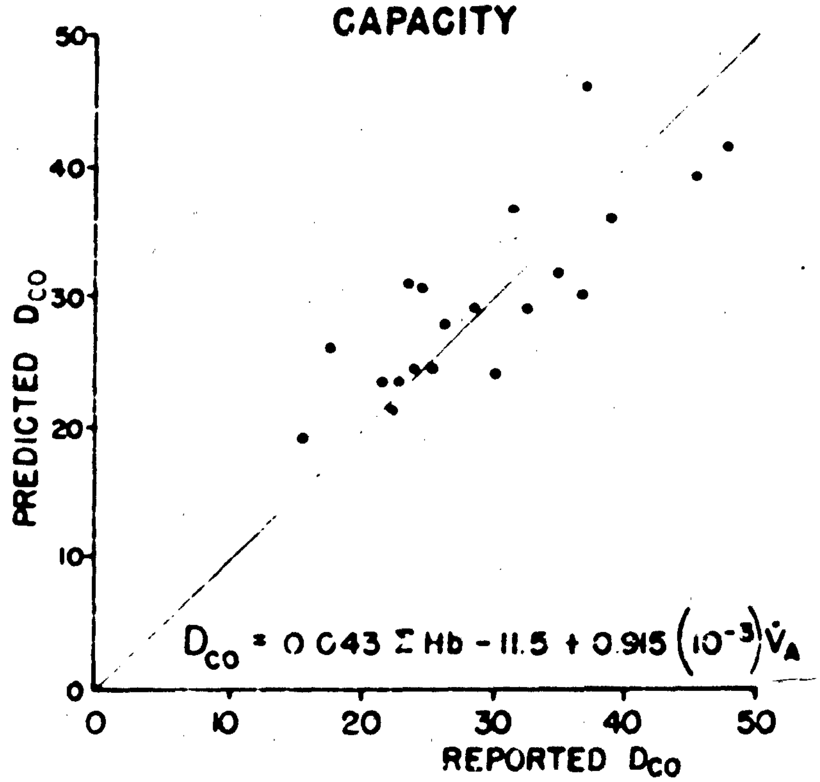


FIG. 5

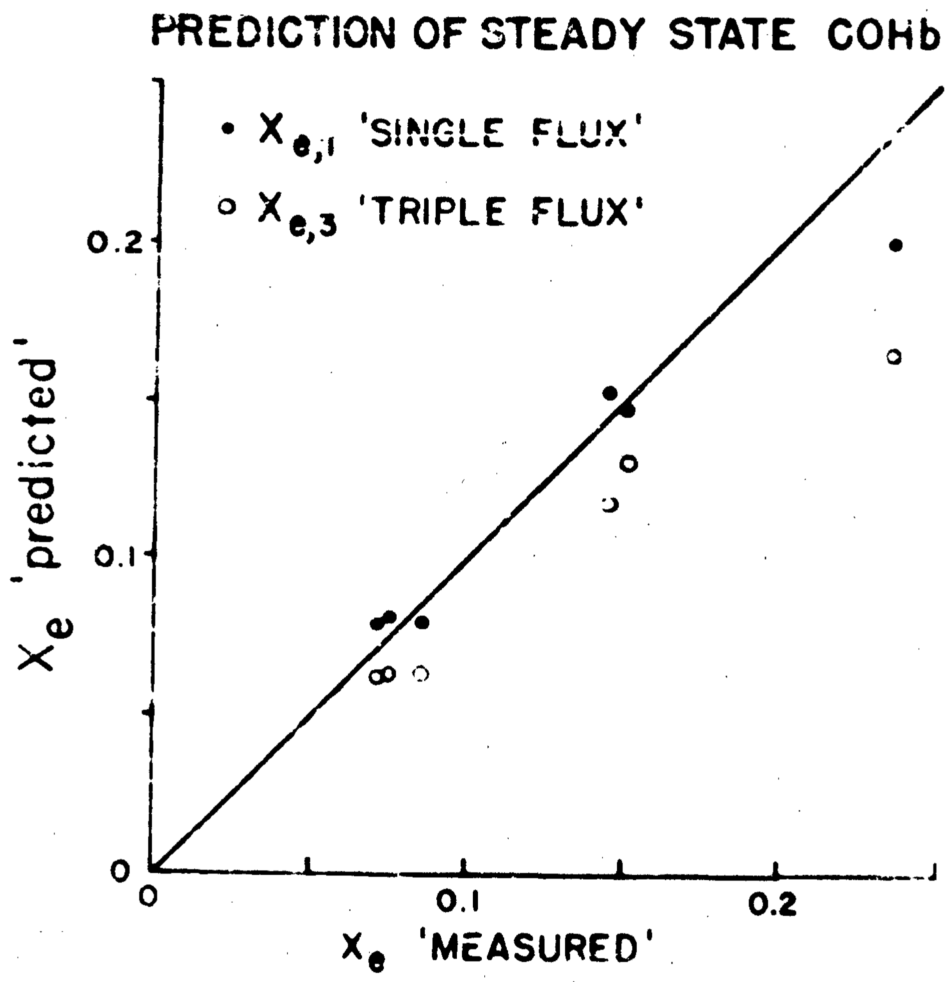

PREDICTION OF STEADY STATE COHb
• $X_{e,1}$ 'SINGLE FLUX'
○ $X_{e,3}$ 'TRIPLE FLUX'
0.2
0.1
0
0
0.1
0.2
X_e 'predicted'
X_e 'MEASURED'

FIG. 6

PREDICTION OF COHb AS A FUNCTION OF TIME

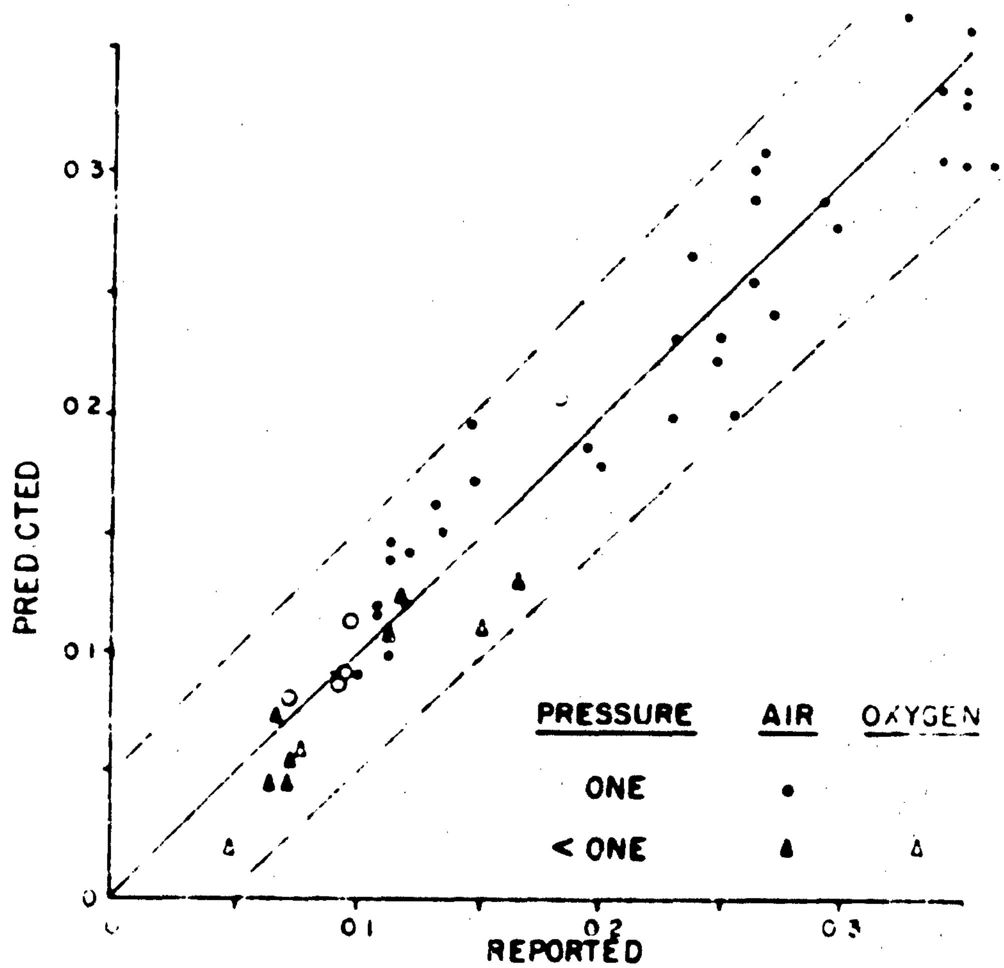


FIG. 7

COHb EQUILIBRA & INSPIRED CO CONCENTRATIONS

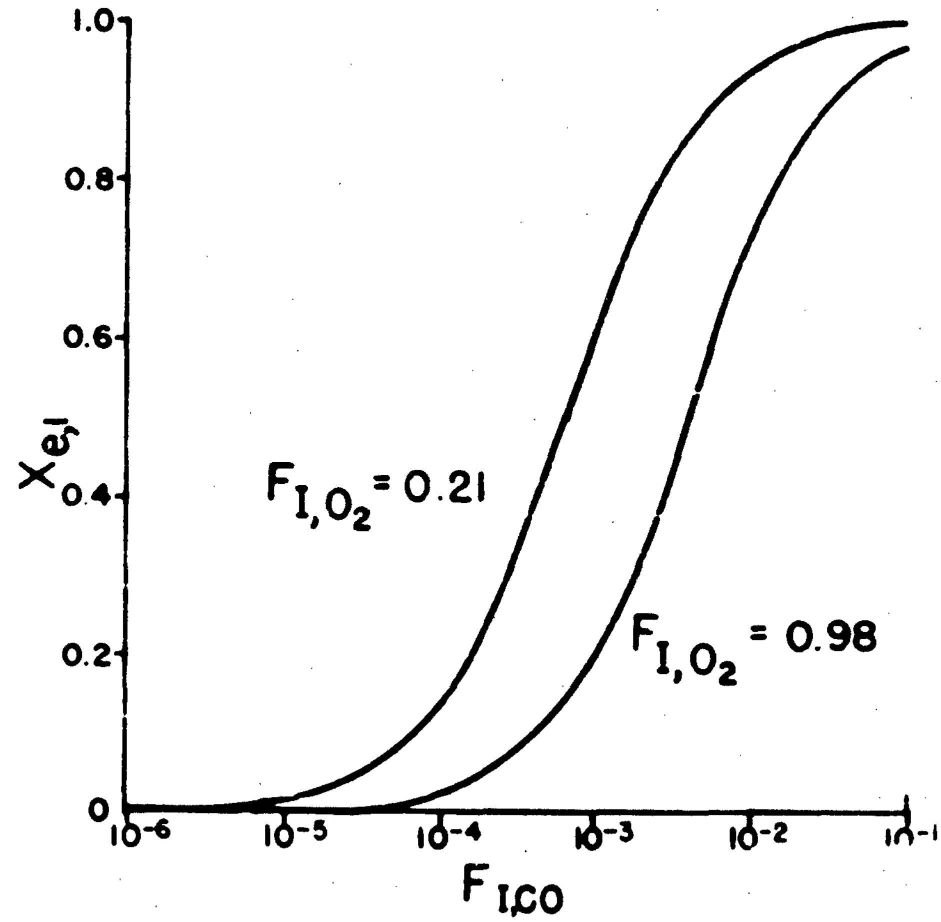


FIG. 8

COHb AT VARIOUS TIMES & INSPIRED CO CONCENTRATIONS

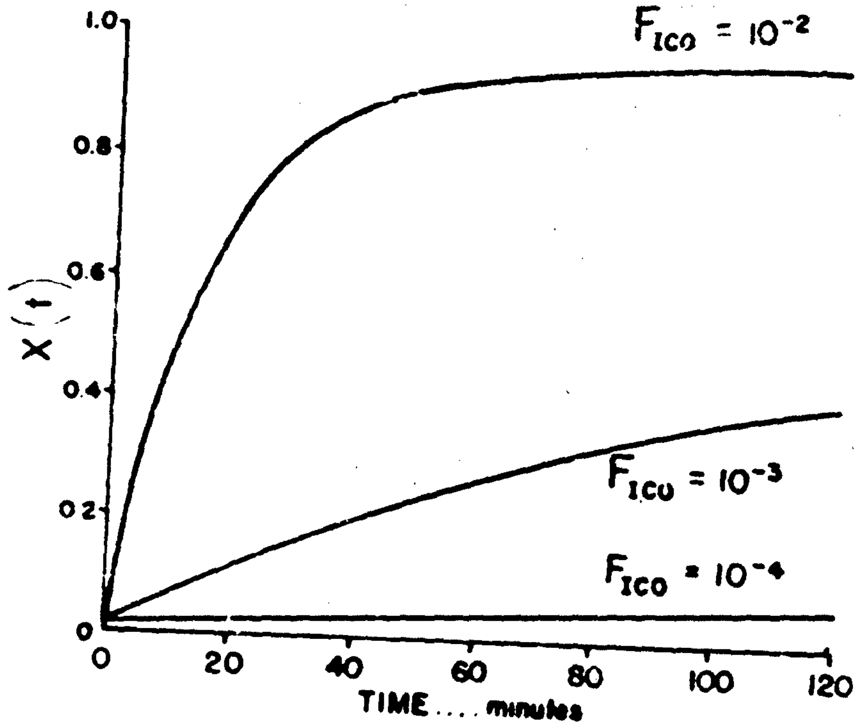


FIG.9

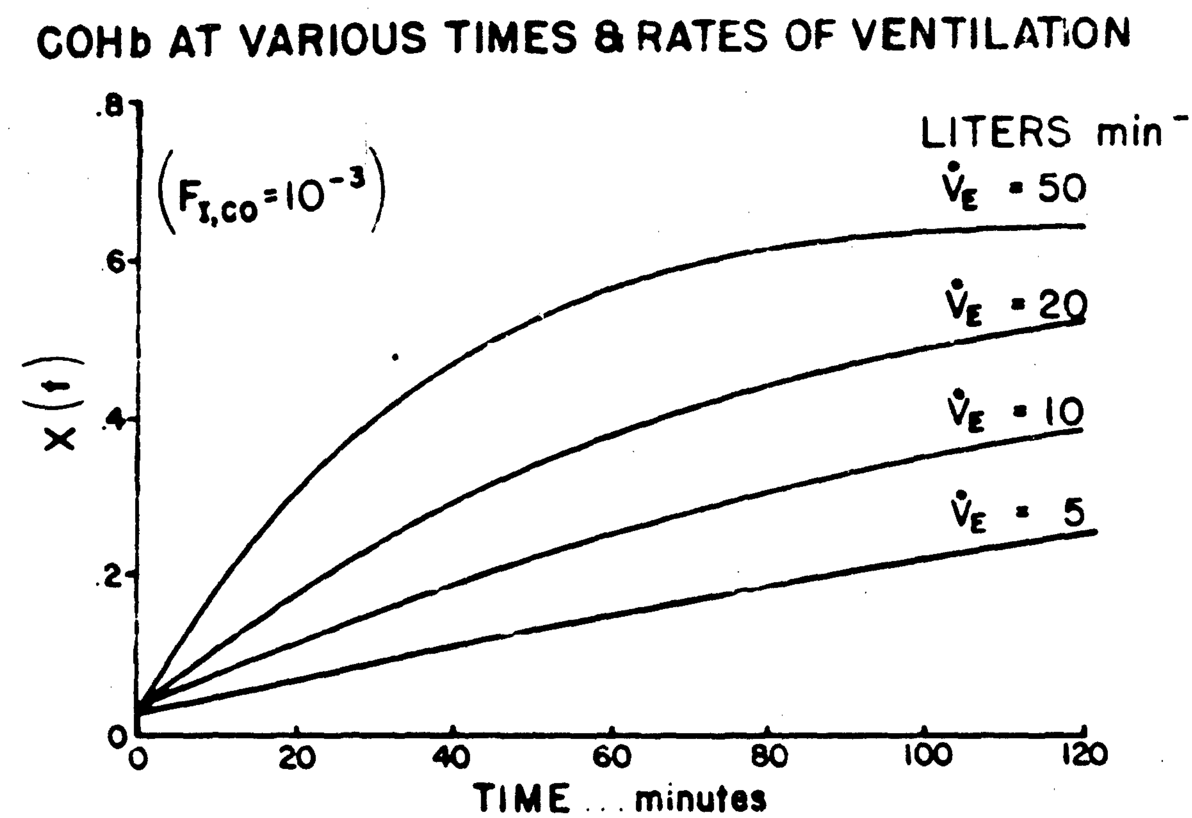

COHb AT VARIOUS TIMES & RATES OF VENTILATION
$(F_{I,CO} = 10^{-3})$
LITERS min⁻
$\dot{V}_E = 50$
$\dot{V}_E = 20$
$\dot{V}_E = 10$
$\dot{V}_E = 5$
X(t)
.8
.6
.4
.2
0
0
20
40
60
80
100
120
TIME ... minutes

FIG. 10

COHb AT VARIOUS . . . S AND QUANTITIES OF HEMOGLOBIN

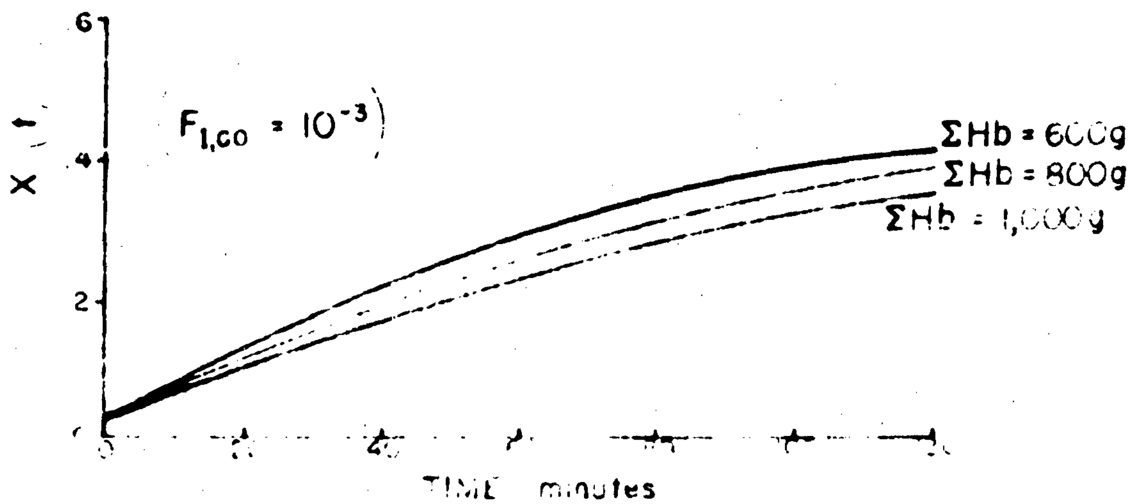
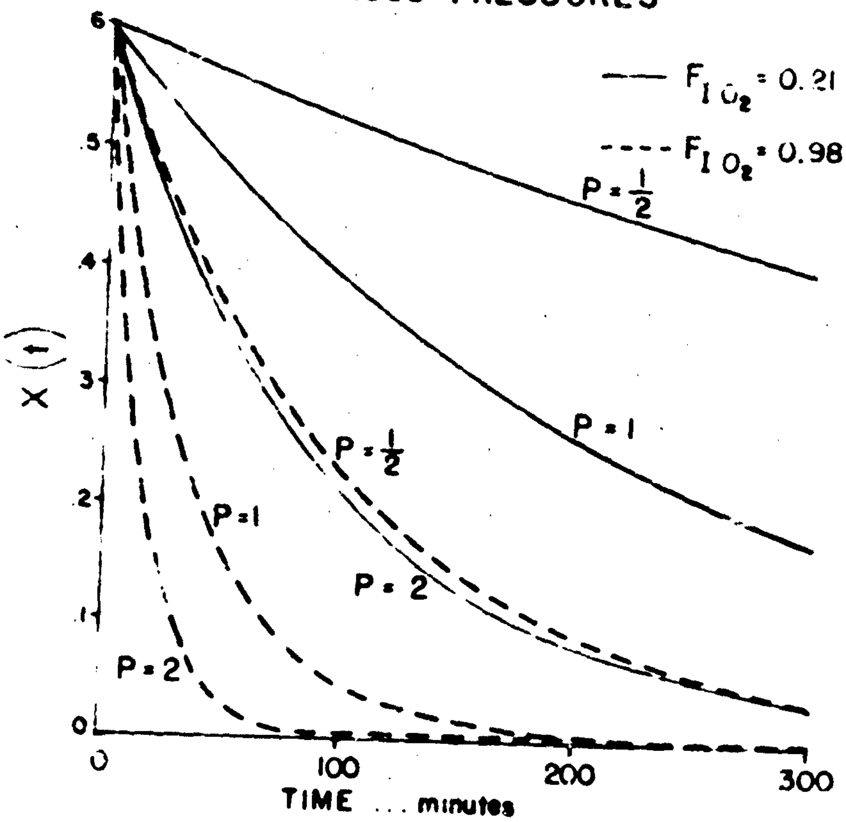


FIG. 11

ELIMINATION OF CO WHEN BREA[illegible]G AIR OR OXYGEN AT VARIOUS PRESSURES



[illegible]

[illegible]

[illegible]

[illegible]